Electrospun polymeric dressings with tuned collagen type I and antimicrobial peptides activities for enhanced wound healing

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Wound dressing is an important segment of the medical and pharmaceutical market worldwide. In the past, traditional dressings were used to simply manage wounds. Nowadays, wound dressings aim faster skin regeneration, oxygen exchange and lower microbial colonization.

Acute wound therapies target specific phases of wound-healing, hemostasis, inflammation, proliferation and maturation, but do not consider possible disrupts on the usual conduct of each phase [1]. Due to a number of potential stimuli, ischemia, bioburden, necrotic tissue, trauma, etc., wounds can stall in one phase of healing, typically inflammation, contributing to wound chronicity [2]. Chronic wounds are often characterized by a defective matrix and cell debris impair healing, high bacteria counts, prolonged inflammation and moisture imbalance. Conventional therapies identify and remove these barriers to wound-healing by applying individualized treatments to each barrier [3].

In the last years, synthetic biodegradable polymeric matrixes, e.g. poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL) and polyurethane (PU), with versatile physical and mechanical properties, have demonstrated wound-healing abilities and enhanced re-epthelialization. The same capacities have been recognized in naturally occurring polymers, like cellulose and collagen [4]. In fact, collagen type I (Col I) has been highlighted as uniquely suited for wound dressing therapies because of its involvement in all phases of wound-healing. Platelets aggregate around exposed collagen and secrete factors that stimulate the intrinsic clotting cascade responsible for a stable hemostatic "plug". In addition, collagen dressings have the ability to absorb wound exudates to maintain a moist environment [5].

Recently, the unique diverse function and architecture of antimicrobial peptides (AMPs) has attracted considerable attention as a tool in the design of molecular templates for new anti-infective drugs. AMPs are gene-encoded short amphipathic molecules with broad-spectrum antimicrobial activity. Some AMPs of mammal and amphibian origins have been identified as promoters of wound-healing activities. LL37 (37 a.a.), the only cathelicidin-derived AMP found in humans, plays a central role in the innate immune response and inflammation [6]. Esculentin-1a(1-21)NH_2 (20 a.a.) derived from the frog skin AMP esculentin-1a [7], and Tiger 17 (11 a.a.) synthesized from tigerinin AMPs [8] are known to act on different phases of wound-healing. Pexiganan (22 a.a.) synthesized from magaining is known to reduce microbial burden without enhancing bacterial resistance [9].

In the present work, we proposed to engineer polymeric wound dressings by electrospinning for acute to chronic wound care that actively stimulate all phases of healing and prevent bacterial colonization. Synthetic and natural polymers (cellulose, PLA, PLGA, PCL and PU) are being electrospun in the form of mats and combined with Col I and AMPs, with immunoregulatory abilities, in one single therapy that will act on all barriers to wound healing: deficient cell matrix and debris

impair healing, prolonged inflammation, high bacteria counts and moisture imbalance. Our strategy is target-directed by tuning the activity of each element composing the dressing.

At the moment, we are in the first stage of our research, in the production of flexible and resistant single and multi-polymer dressings cross-linked with Col I by electrospinning. Different ranges of processing and solution conditions were tested: applied voltage (15-30 kV), flow rate (1-4 mL/h), distance to collector (10-15 cm), environment temperature (13-25ºC), polymer concentration, viscosity, solvent volatility, surface tension and conductivity. Regardless the polymer used, the conditions were defined to obtain high, interconnected porosity and large surface area to allow both oxygen exchanges and exudates absorbency. Once we attained the proper dressings, the second stage, which consists in the covalent immobilization of the AMPs and posterior *in vitro* and *in vivo* testing, will start. This is a multidisciplinary project that is progressing very quickly. We are confident that multiple and viable solutions for wound care, with great potential to the biomedical field, will result from this strategy.

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